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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER

ART UNIT	PAPER NUMBER
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DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/462,846

Applicant(s)

ESTELL DAVID A

Examiner

David J. Steadman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 1-17 is/are pending in the application.
- 4a) Of the above claim(s) 2, 3, and 10-12 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) 1, 4-9, and 13-17 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claims ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☐ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____
- 18) ☐ Interview Summary (PTO-413) Paper No(s) ____
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other: ____

DETAILED ACTION

Status of the Application

Claims 1-17 are pending in the application.

Applicants' election without traverse of Group I, claims 1, 4-9, and 13-17, drawn to a microorganism having a mutation or deletion of the gene encoding cysteine protease-1 (CP1) and methods for the production of a heterologous protein using a microorganism having a mutation or deletion in the gene encoding CP1 in Paper No. 9, filed 04/25/01 is acknowledged.

Claims 2, 3, and 10-12 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Drawings

1. The drawings submitted with this application have not been reviewed by a draftsman at this time. When formal drawings are submitted, the draftsman will perform a review. Direct any inquiries concerning drawing review to the Drawing Review Branch (703) 305-8404.

Claim Objections

2. Claims 1 and 15 are objected to because of the recitation of "CP1", "apr", "npr", "epr", "wpr", and "mrp." Abbreviations, unless otherwise obvious and or commonly used in the art, should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used. Appropriate correction is required.

3. Claims 4 and 6 are objected to because they depend on non-elected claims 2 and 3.

4. Claims 1, 9, and 16 are objected to because of the following informalities: the terms "encoding CP1 said mutation" in claim 1, "consisting of a proteases" in claim 9, and "having at mutation" in claim 16 are grammatically incorrect and should be replaced with, for example, "encoding CP1, said mutation", "consisting of proteases", and "having a mutation", respectively. Appropriate correction is required.

5. Claims 13(a) and 16 are objected to because of the recitation of "cysteine protease 2 and cysteine protease 3" in claim 13(a) and "CP2, CP3" in claim 16, which is non-elected subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Regarding claim 9, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

8. The term "selected from the group consisting of: a proteases, carbohydrases, and lipases; isomerases such as racemases, epimerases, tautomerases, or mutases; transferases, kinases and phosphatases" in claim 9 is unclear and confusing. It is suggested that the language be replaced with a term that has a more clearly identifiable meaning, for example, "selected from the group

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consisting of: proteases, carbohydrases, lipases, isomerases, epimerases, tautomerases, mutases, transferases, kinases, and phosphatases."

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 6-9, 13, and 15-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 (claims 6-9 dependent thereon), 13, and 15-17 are rejected because the claims recite a gram-positive microorganism having a mutation or deletion of part or all of the gene encoding CP1 resulting in the inactivation of the CP1 proteolytic activity (claim 1), a method for producing a heterologous protein using a *Bacillus* host cell with a mutation or deletion in at least one of the genes encoding CP1 (claim 13) and, alternatively, at least one of the genes encoding apr, npr, epr, wpr, and mrp (claim 15), or a gram-positive microorganism having a mutation or deletion of the gene encoding CP1 (claim 16) and at least one of the genes encoding apr, npr, epr, wpr and mrp (claim 17). The specification teaches only one representative species of such microorganisms or *Bacillus* host cells, namely, *Bacillus subtilis* with a mutation or deletion in the gene encoding CP1, resulting in the inactivation of CP1 proteolytic activity. The specification fails to disclose any other microorganisms by any identifying structural characteristics or properties other than the functionality of having a mutation or deletion of part or all of the gene

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encoding CP1 resulting in the inactivation of the CP1 proteolytic activity or the functionality of having a mutation or deletion of part or all of the gene encoding CP1. Given the lack of description of additional representative species of microorganisms as encompassed by the genus of the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise and exact terms that a skilled artisan would recognize that Applicants were in possession of the claimed invention.

10. Claims 1, 6-9, 13, and 15-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a *Bacillus* host cell with a mutation or deletion in the gene encoding CP1, *resulting in the inactivation of CP1 proteolytic activity* and a method for producing heterologous proteins using said *Bacillus* host cell, does not reasonably provide enablement for any gram-positive microorganism having a mutation or deletion of part or all of the gene encoding CP1 resulting in the inactivation of the CP1 proteolytic activity (claim 1), any gram-positive microorganism having any mutation or deletion of the gene encoding CP1 (claim 16), and alternatively, having a mutation or deletion in at least one of the genes encoding apr, npr, epr, wpr, and mrp (claim 17), or a method of producing a heterologous protein using a *Bacillus* host cell having any mutation or deletion in at least one of the genes encoding CP1 (claim 13) and, alternatively, comprising any mutation or deletion in at least one of the genes encoding apr, npr, epr, wpr, and mrp (claim 15). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1 (claims 6-9 dependent thereon), 13, and 15-17 are so broad as to encompass any gram-positive microorganism having a mutation or deletion of part or all of the gene encoding

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CP1 resulting in the inactivation of the CP1 proteolytic activity, any gram-positive microorganism having any mutation or deletion of the gene encoding CP1, and alternatively, having any mutation or deletion in the genes encoding apr, npr, epr, wpr, and mrp, and a method of producing a heterologous protein using a gram-positive host cell having any mutation or deletion in at least one of the genes encoding CP1 and, alternatively, comprising any mutation or deletion in at least one of the genes encoding apr, npr, epr, wpr, and mrp. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of gram-positive microorganisms or microorganisms having mutations or deletions of the genes encoding CP1, apr, npr, epr, wpr, and mrp as encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to a *Bacillus* host cell with a mutation or deletion in the gene encoding CP1, *resulting in the inactivation of CP1 proteolytic activity*.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art

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would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass any gram-positive microorganism having a mutation or deletion of part or all of the gene encoding CP1 resulting in the inactivation of the CP1 proteolytic activity, any gram-positive microorganism having any mutation or deletion of the gene encoding CP1, and alternatively, having any mutation or deletion in the genes encoding apr, npr, epr, wpr, and mrp, and a method of producing a heterologous protein using a gram-positive host cell having any mutation or deletion in at least one of the genes encoding CP1 and, alternatively, comprising any mutation or deletion in at least one of the genes encoding apr, npr, epr, wpr, and mrp because the specification does not establish (A) which gram-positive microorganisms comprise a gene expressing CP1; (B) the ability of any gram-positive microorganism to function with a deletion in the gene encoding CP1 or a deletion of CP1 in combination with mutations or deletions of the genes encoding apr, npr, epr, wpr, and mrp as there is very little prior art regarding the biological function of this enzyme in gram-positive microorganisms and the result of deleting the gene is unpredictable; (C) regarding claims 13 and 15-17, regions of the CP1, apr, npr, epr, wpr, and mrp protein structures which may be mutated with an expectation of obtaining the desired biological activity; (D) regarding claims 13 and 15-17, the general tolerance of CP1, apr, npr, epr, wpr, and mrp to modification and extent of such tolerance; (E) regarding claims 13 and 15-17, a rational and predictable scheme for modifying any CP1, apr, npr, epr, wpr, and mrp residues with an expectation of obtaining the desired biological function; and (F) the specification provides

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insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any gram-positive microorganism having a mutation or deletion of part or all of the gene encoding CP1 resulting in the inactivation of the CP1 proteolytic activity, any gram-positive microorganism having any mutation or deletion of the gene encoding CP1, and alternatively, having any mutation or deletion in the genes encoding apr, npr, epr, wpr, and mrp, and a method of producing a heterologous protein using a gram-positive host cell having any mutation or deletion in at least one of the genes encoding CP1 and, alternatively, comprising any mutation or deletion in at least one of the genes encoding apr, npr, epr, wpr, and mrp. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Conclusion

11. No claim is in condition for allowance.

Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4242. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE

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COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Steadman, whose telephone number is (703) 308-3934. The examiner can normally be reached Monday-Friday from 8:00 am to 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Art Unit receptionist whose telephone number is (703) 308-0196.

David J. Steadman

Rebecca P. Priddy
REBECCA S. PRIDDY
PRIMARY EXAMINER
308-3804
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